

Uptake pattern of ⁶⁸Ga- DOTA-NOC in tissues: implications for inflammatory diseases

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Abstract :

Objectives: ⁶⁸Ga-DOTA-NOC binds to somatostatin receptor (SSTR) subtypes 2 and 5, also expressed on lymphocytes and macrophages, but no information is available about uptake in tissues that might be affected by a chronic inflammatory process. Our aim was to obtain normal reference values for ⁶⁸Ga-DOTA-NOC uptake in tissues prone to chronic inflammation. **Methods:** Retrospective study in 81 patients in whom the scan was performed for a suspicion of neuroendocrine tumor (NET). We analyzed major joints, salivary glands, thyroid, aortic wall from images acquired

after injection of $173,9 \pm 1$ Mbq of ^{68}Ga -DOTA-NOC. We calculated the SUV_{max} and $\text{SUV}_{\text{target}}/\text{SUV}_{\text{gluteus}}$ ratio or $\text{SUV}_{\text{target}}/\text{SUV}_{\text{aorta}}$ ratio. Data are reported as mean ± 2 or ± 3 standard deviations (SD).

Results: SUV_{max} appeared more reliable than other ratios. In thyroid we found a mean SUV_{max} of 1.36 ± 0.45 , with no values $> 3\text{SD}$; in parotid glands 0.98 ± 0.40 , with 2 values $> 3\text{SD}$; in submandibular glands 0.99 ± 0.37 , with 2 values $> 3\text{SD}$; in aortic arch 1.71 ± 0.50 , with 1 value $> 3\text{SD}$; in thoracic aorta 2.03 ± 0.52 , with 1 value $> 3\text{SD}$; in abdominal aorta 2.19 ± 0.49 , with no value $> 3\text{SD}$; in shoulders 0.92 ± 0.31 and in hips 0.87 ± 0.34 , with 2 and 4 values $> 3\text{SD}$, respectively. These 12 values with $\text{SUV}_{\text{max}} > 3\text{SD}$, belong to 5 patients, 3 of which had signs of xerostomia and/or arthritis. A statistically significant correlation was observed between SUV_{max} and age in all examined tissues but in the aorta. **Conclusions:** Tissues in which lymphocytic infiltration may occur show that SUV_{max} is tissue-dependent. Within tissue variability, an SUV_{max} higher than the mean $+3\text{SD}$ is rarely found amongst patients without a symptomatic chronic inflammatory process but, when found, may highlight a chronic inflammatory condition.

Keywords: somatostatin receptors, ^{68}Ga -DOTA-NOC, inflammation, autoimmune diseases

Introduction

Somatostatin (SST) is a neuropeptide with a very short lifespan secreted in the central nervous system, endocrine glands and gastrointestinal tract where it acts primarily to inhibit neuro-transmission. It interacts with five different subtypes of somatostatin receptors (SSTR 1-5) that belong to the G-coupled seven transmembrane spanning receptor domain family and they are expressed on the surface of many cells and organs (1).

Nuclear medicine offers a panel of radiopharmaceuticals for both gamma-camera and PET studies that provide functional information on body distribution of SST. Small structural modifications, chelator substitution or metal replacement, are known to affect the binding affinity of the molecule to the receptors (2). These radiopharmaceuticals are currently used for diagnosis and follow-up of different pathological conditions characterized by an overexpression of SSTR on their cell surface. The use of radiolabelled SST analogues for diagnosis and therapy follow-up of NETs is nowadays well consolidated and also there is evidence about the utility of these methods in different clinical settings(3) , in particular chronic inflammatory diseases not only in the diagnostic approach but in monitoring therapy outcome (4). Somatostatin receptor scintigraphy (SRS), mainly using SST analogues labeled with Indium-111 or Tc-99m, have been extensively performed in diagnosis and follow-up of chronic inflammatory diseases such as Rheumatoid Arthritis (RA), Sjögren's Syndrome and others (5) , in addition to NETs (6,7), despite normal values of SST uptake in non-neoplastic tissues is poorly known.

In the last 16 years, the better anatomical detail, spatial resolution and diagnostic accuracy of PET/CT, together with the availability of Ge-68/Ga-68 generators, has lead to the development of ⁶⁸Ga conjugated peptides (-NOC, -TOC, -TATE) that differ for the affinity to SSTR subtypes: ⁶⁸Ga-DOTA-TOC is more selective for receptors 2 and 5, ⁶⁸Ga-DOTA-TATE for type 2 receptor (8-10) and ⁶⁸Ga-DOTA-NOC shows high affinity for SSTR-2 and 5 (11).

Because it has been observed that SSTR-2 and 5 are over-expressed by inflammatory cells (12), radiolabelled DOTA-NOC results an attractive molecule for imaging inflammatory conditions. Despite normal biodistribution pattern of DOTA-

NOC has been extensively described for tumour conditions little information is available about uptake values in tissues that may be potentially affected by an inflammatory diseases (13). Prasad et al. (14) evaluated the uptake in normal organs and tumour lesions with ^{68}Ga -DOTA-NOC in 89 patients with neuroendocrine tumours. Among the examined tissue they evaluated SUV_{max} in thyroid (3.4 ± 1.4). Boy and colleagues (15) studied 120 patients with ^{68}Ga -DOTA-TOC and they described the mean SUV_{max} value for thyroid and parotid glands and found statistically significant gender difference in thyroid. Castellucci et al. measured the extra tumoral uptake of ^{68}Ga -DOTA-NOC only in the pancreatic head and found large variability amongst patients (16).

As the demand of ^{68}Ga -DOTA-NOC PET studies increase for inflammatory conditions, it becomes important to know the normal distribution pattern of this molecule and to quantify the uptake in tissues that can potentially be affected by a chronic inflammatory condition in order to correctly interpret the images in patients with such disorders.

The aim of this study was, therefore, to evaluate the uptake (SUV_{max}) of ^{68}Ga -DOTA-NOC in normal tissues that could be potentially involved in chronic inflammatory diseases to identify a cut off value for SUV_{max} that could help to differentiate between physiologic or pathologic conditions. In particular we measured the ^{68}Ga -DOTA-NOC uptake in parotid glands, submandibular glands (sites of sialoadenitis), in thyroid (site of thyroiditis), in shoulders and hips (sites of chronic arthritis), aortic wall (site of large vessel vasculitis and atherosclerosis).

Materials and methods

Study design

We conducted a retrospective observational study including 84 studies performed with ^{68}Ga -DOTA-NOC PET/CT in the Nuclear Medicine Unit of S. Andrea Hospital, "Sapienza" University of Rome between May 2012 and April 2013.

Study population

Inclusion criteria for this study were: patients with a recent ^{68}Ga -DOTA-NOC PET/CT scan; patients without specific symptoms or clinically diagnosed dysfunction of salivary glands, thyroid, joints and large vessels; age between 30 and 80 years. Exclusion criteria were: patients with diffused neoplastic disease; patients with metastatic cancer adjacent to one of the examined tissues.

All patients had no anamnestic record of autoimmune/inflammatory conditions affecting the salivary glands, thyroid, joints or large vessels.

Study protocol

The Ga-68 was eluted from a Ge-68/Ga-68 generator and bound to DOTA-NOC (ABX, Austria) in compliance with the GMP regulations. Whole body scans were acquired with a dedicated hybrid PET/CT tomograph (Phillips) one hour after intravenous injection of 173.9 ± 1 Mbq of ^{68}Ga -DOTA-NOC. PET images were acquired for 3-4 minutes per bed position from head to mid-thigh. A low-dose CT scans for attenuation correction and anatomic location was also performed. Images were downloaded from the hospital database and interpreted as positive or negative by 3 expert nuclear medicine physicians (LKA, CL, CEG).

In all images we calculated the maximum standardized uptake value (SUV_{max}), (T/B) ratio using gluteus muscle ($\text{SUV}_{\text{target}}/\text{SUV}_{\text{gluteus}}$) or the lumen of thoracic aorta ($\text{SUV}_{\text{target}}/\text{SUV}_{\text{aorta}}$) in several tissues that could potentially be involved by a chronic inflammatory/autoimmune process.

In particular, salivary glands (parotid and submandibular) because of potential sialoadenitis; thyroid because of thyroiditis; thoracic and abdominal aorta because of potential large vessel vasculitis; shoulder and hip joints for potential chronic arthritis. In symmetrical organs the SUV_{max} were calculated for both left and right side.

The obtained values from the three methods were compared between them.

Statistical analysis: demographics and descriptive statistics were analyzed using Stata version 14. The association between SUV_{max} or T/B values and the age were explored with a multiple linear regression with categorical variables model.

Differences between gender, treatment, and positivity of the scan, were analyzed by Student t test. Two and three standard deviations above the mean identified values above the 95th and 97.5th percentile respectively. A SUV_{max} or T/B value was considered abnormal if it was greater than the mean +3SD.

End point: to identify a SUV_{max} or SUV_{target}/SUV_{gluteus} or SUV_{target}/SUV_{aorta} cut-off as reference for each tissue to be used to identify pathological tissues in future studies in patients affected by chronic inflammatory processes.

Results

We analyzed 84 patients who performed ⁶⁸Ga-DOTA-NOC PET/CT between May 2012 and April 2013 because of a confirmed or suspected neuroendocrine tumour. Three patients with diffuse neoplastic disease that could potentially interfere with SUV_{max} calculation in tissues due to a “partial volume effect” were excluded from the study. Out of the recruited 81 patients, 9 had previous thyroidectomy and therefore the uptake in thyroid was not available. Main results are summarized in tables 1 and 2. Average age of patients was 57.5 ± 13.2 years and 56.8% were females. Gastro-entero-pancreatic neuroendocrine tumours were the most frequent indication for the nuclear medicine study (58.1%), followed by lung carcinoids (14.8%). In 42 patients (51.9%) the scan was considered positive for pathologic NETs-associated expression of SSTRs and 39 patients (48.1%) were completely normal. Twenty-two patients were under treatment with long-acting somatostatin analogues.

Table I**Patients' clinical characteristics**

Patient's data (n=81)	
Mean age \pm standard deviation	57.5 \pm 13.2
Sex	
Females	46 (56.8%)
Indication	
Gastrointestinal tumour	28 (34.6%)
Pancreatic tumor	19 (23.5%)
Lung carcinoid	12 (14.8%)
Unknown NET	7 (8.6%)
Others	4 (4.9%)
MEN1	2 (2.5%)
Thyroid medullary cancer	9 (11.1%)
Patients with positive scan	42 (51.9%)
Patients in therapy with SST analogues	22 (27.1%)

Table II

Tissues with [68Ga]Ga-DOTA-NOC uptake greater than mean +2SD or +3SD

Tissue	SUV _{max} mean (SD) median [range]	SUV _{max} >2SD <3SD n (%)	SUV _{max} / SUV _{gluteus} >2SD <3SD n (%)	SUV _{max} / SUV _{aorta} >2SD <3SD n (%)	SUV _{max} >3SD n (%)	SUV _{max} / SUV _{gluteus} >3SD n (%)	SUV _{max} / SUV _{aorta} >3SD n (%)
Hips (n=81)	0.87 (0.35) 0.82 [0.37-2.42]	4 (4.9%)	4 (4.9%)	2 (2.5%)	4 (4.9%)	2 (2.5%)	3 (3.7%)
Shoulders (n=81)	0.92 (0.32) 0.88 [0.28-2.48]	6 (7.4%)	5 (6.2%)	3 (3.7%)	2 (2.5%)	1 (1.2%)	2 (2.5%)
Parotid glands (n=81)	0.99 (0.40) 0.91 [0.22-2.70]	3 (3.7%)	6 (7.4%)	4 (4.9%)	2 (2.5%)	0 (0%)	1 (1.2%)
Submandibular glands (n=81)	0.99 (0.37) 0.96 [0.02-2.55]	1 (1.2%)	1 (1.2%)	5 (6.2%)	2 (2.5%)	2 (2.5%)	1 (1.2%)
Thyroid (n=72)	1.36 (0.45) 1.34 [0.28-2.66]	5 (6.9%)	4 (5.5%)	4 (5.5%)	0 (0%)	2 (2.7%)	1 (1.4%)
Aortic arch (n=81)	1.71 (0.50) 1.71 [0.53-3.46]	1 (1.2%)	1 (1.2%)	2 (2.5%)	1 (1.2%)	0 (0%)	1 (1.2%)
Thoracic aorta (n=81)	2.03 (0.52) 2.01 [0.99-3.89]	2 (2.5%)	1 (1.2%)	0 (0%)	1 (1.2%)	1 (1.2%)	2 (2.5%)
Abdominal aorta (n=81)	2.19 (0.49) 2.21 [1.05-3.46]	2 (2.5%)	1 (1.2%)	3 (3.7%)	0 (0%)	2 (2.5%)	2 (2.5%)

n=number of values, SUV_{max}=maximum Standardised Uptake Value.

A total of 1125 ROIs in 12 tissues (and 2 background areas) were examined for the 81 cases. The distribution of SUV_{max} values in the tissues is shown in figure 1A. Lowest mean values were observed in hips, shoulders and salivary glands as compared to thyroid and aortic wall. Thirty-six values, belonging to 18 patients, exceeded the mean of SUV_{max} +2SD and 12 values, belonging to 5 patients exceeded the mean +3SD (4 hips, 2 shoulders, 2 parotids, 2 submandibular glands, 1 aortic arch and 1 thoracic aorta).

When we analyzed data of SUV_{target}/SUV_{gluteus} ratios (Figure 1B), we found 33 values, belonging to 21 patients, exceeding the mean +2SD and 10 values, belonging to 7 patients exceeding the mean +3SD (2 hips, 1 shoulders, 2 submandibular glands, 2 thyroid, 1 thoracic aorta and 2 abdominal aorta).

Similarly, data of SUV_{target}/SUV_{aorta} ratios, showed 36 values, belonging to 23 patients, exceeding the mean +2SD and 13 values, belonging to 8 patients exceeding the mean +3SD (3 hips, 2 shoulders, 1 parotids, 1 submandibular glands, 1 thyroid, 1 aortic arch, 2 thoracic aorta and 2 abdominal aorta), as shown in figure 1C.

Figure 1

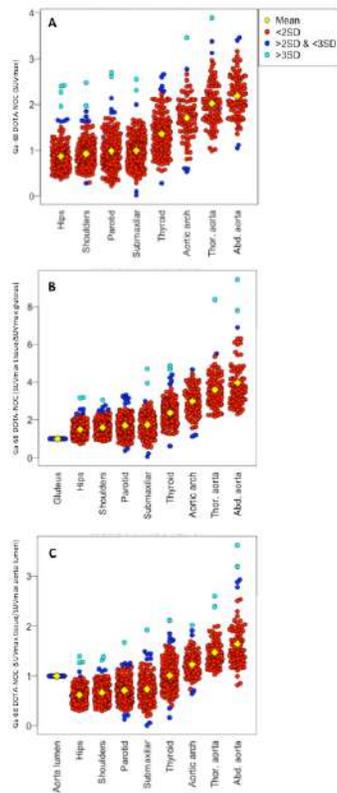


Figure 1. **Distribution of ^{68}Ga -DOTA-NOC in tissues.** A) SUV_{max} values in all the examined tissues. For hips, shoulders, parotid glands, submandibular glands and thyroid two measurements (left and right) were performed for each patient. B) Distribution of ratio SUV_{max} in tissue/ SUV_{max} in gluteus muscle. C) Distribution of ratio SUV_{max} in tissue/ SUV_{max} in aortic lumen. Yellow diamonds represent the mean. Dark blue and cyan circles represent the mean $\pm 2\text{SD}$ and $\pm 3\text{SD}$ respectively.

Of the 18 patients with SUV_{max} above the mean $+2\text{SD}$, only 5 had multiples sites of increased uptake (figure 2). Fifteen of these 18 patients accepted to have a biochemical and clinical screening for chronic inflammatory diseases (including rheumatology, immunology and endocrinology test). Only three subjects showed signs but no symptoms suggestive for arthritis or xerostomia (1 with $\text{SUV}_{\text{max}} >3\text{SD}$ in joints; 1 with $\text{SUV}_{\text{max}} >3\text{SD}$ in salivary glands; 1 with $\text{SUV}_{\text{max}} >3\text{SD}$ in both joints, and salivary glands) but laboratory tests were negative in all of them. (Figures 3,4) Linear regression analyses showed that age and SUV_{max} were positively significantly correlated (corr. coeff. 0.001; $p < 0.01$) in all tissues except abdominal aorta. SUV_{max}

mean in the tissues where not significantly correlated with sex, SST treatment (that may compete with DOTA-NOC) or scan positivity (reflecting underlying NET activity). The Spearman value between the three methods for analysing all tissues showed values greater than 0.85 between the global SUV_{max} method and the $SUV_{target}/SUV_{gluteus}$ for all tissues but aorta.

Discussion

In the present study we quantified the uptake of ^{68}Ga -DOTA-NOC in tissues that could be affected by chronic inflammatory process. To our knowledge this is the first report that analyses these tissues by SRS in normal subjects.

Patients were recruited based on the absence of any specific symptom and absence of any clinically diagnosed disease of salivary glands, thyroid, joints and large vessels. All patients with reported xerophthalmia, xerostomia, thyroiditis, hypo or hyperthyroidism, arthritis or any kind of vasculitis were excluded from this study. Nevertheless, we did not measure autoantibody titres in all patients, but only in 15 of the 18 patients who showed a high ^{68}Ga -DOTA-NOC uptake in some of the target tissues. This may be a limitation of our study but being a retrospective study, we had no possibility to access to all patients but only anamnestic data were available. Therefore, we cannot exclude that some of the patients with a low tissue uptake might have some autoantibody and an underlying autoimmune phenomenon. On the other hand, we did not aim at evaluating the sensitivity and specificity of ^{68}Ga -DOTA-NOC scan for autoimmune/inflammatory conditions in normal subjects, but rather we aimed at describing the range of uptake in tissues in a population without clinical signs or symptoms of autoimmune/inflammatory conditions.

The highest uptake value was found in the abdominal aorta followed by the thyroid gland, possibly explained by the presence of activated macrophages in atherosclerotic plaque as suggested by some authors (17) and the presence of lymphocytes with somatostatin receptors in thyroid gland (18). These values were not different among patients with or without a positive SRS for NETs, suggesting that the normal uptake pattern, in the examined tissues, is unaffected by the presence of tumour activity.

To quantify the radiopharmaceutical uptake in each tissue we used three different methods: SUV_{max} ; $SUV_{target}/SUV_{gluteus}$ ratio as a subtraction of background activity; $SUV_{target}/SUV_{aorta-lumen}$ ratio as a subtraction of blood pool activity. We found a good correlation (Spearman values >0.85) between the three methods in all tissues, but in aortic segments. Therefore we could propose to use the global SUV_{max} method as an easy, simple and reproducible way to quantify the radiopharmaceutical uptake in all tissues but aortic wall, in which the measurement of $SUV_{target}/SUV_{aorta-lumen}$ ratio is more appropriate to subtract circulating activity.

Out of 81 patients, we found 5 patients with multiple sites of increased uptake and 3 of them had signs, but not symptoms, of impaired salivary gland function or arthrosis, despite the absence of specific auto-antibodies.

We cannot conclude that SRS can detect early inflammatory diseases by this study and an appropriate study should be designed to evaluate the role of SRS in these chronic disorders. In this context, our results are of relevance because they provide a standard reference of SST uptake in normal tissues with possible involvement of chronic inflammatory disorders, to be used to identify patients with pathological uptake.

As we know autoimmune or chronic inflammatory diseases are characterized by phases of exacerbation and quiescence. Clinical and biochemical findings may be present or not and the use of SRS could help to objectively identify patients with a pathological lympho monocitic infiltration in tissues (19).

Prasad et al. (14) in 2010 reported higher SUV_{max} values, than ours, of ^{68}Ga -DOTA-NOC in thyroid (4.7 ± 2.2 vs 1.36 ± 0.45) and in parotid glands (1.9 ± 0.6 vs 0.98 ± 0.4). Also Kuyumcu et al.(20), using ^{68}Ga -DOTA-TATE, found a SUV_{max} in normal thyroid of 4.18 ± 1.9 . However, neither Prasad or Kuyumcu tested their patients for auto-antibodies and we cannot exclude the presence of patients with thyroiditis or Sjögren's syndrome amongst them, that have raised the level of SUV_{max} in glands. The main limitation of our study is the retrospective analysis of a population with oncologic disease, some under treatment with SST analogues. However, we did not find any significant difference between patients with and without an SRS positive tumor or between patients treated and non-treated with SST analogues. The number

of examined patients may appear too exiguous to carry out definitive conclusions although the small standard deviation values found for each tissue, encourage to sustain the correctness of the sample size.

This study is the first that examine the biodistribution of ^{68}Ga -DOTA-NOC in normal salivary glands, thyroid, major joints and aortic wall, thus providing as future research directions a reference for further studies in patients affected by chronic inflammatory disorders or with a suspicion of it.

Figure 2

Figure 2. An example of a patient with uptake levels in thyroid gland higher than population mean +2SD. This patient had no signs or symptoms of thyroid dysfunction neither the presence of autoantibodies.

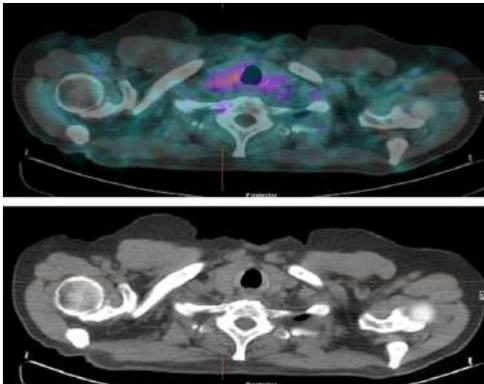


Figure 2. An example of a patient with uptake levels in thyroid gland higher than population mean +2SD. This patient had no signs or symptoms of thyroid dysfunction neither the presence of autoantibodies.

Figure 3

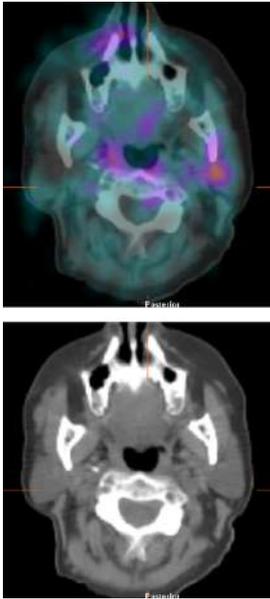


Figure 3. An example of a patient with uptake levels in left parotid gland higher than population mean +3SD. This patient had signs of xerostomia but no symptoms nor autoantibodies. The rheumatologist asked for a salivary gland scintigraphy that showed mild impairment of parotid function.

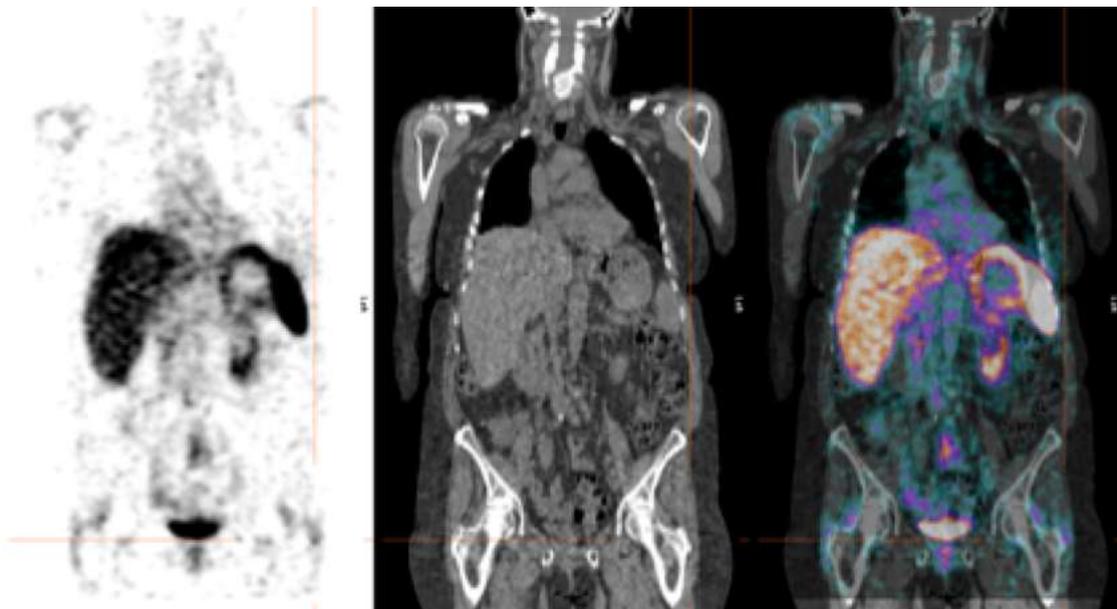


Figure 4. An example of a patient with uptake levels in shoulders and hips higher than population mean +2SD. This patient had inducible pain in joints but no symptoms nor autoantibodies. He was diagnosed with initial arthropathy.

Conclusions

We quantified the uptake of ^{68}Ga -DOTA-NOC in different tissues that might be affected by a chronic inflammation. These values could be used to identify the cut-off to discriminate between normal or pathological condition in a ^{68}Ga -DOTA-NOC PET/CT and to monitor the course of autoimmune or chronic inflammatory diseases.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contribution

All authors equally contributed: Formal analysis, Luz Kelly Anzola and Alberto Signore; Investigation, Carlos Granados and Bruno Lagana; Resources, Chiara Lauri; Supervision, Alberto Signore; Writing – original draft, Luz Kelly Anzola.

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